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(Signature)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hans Reichenbach *et al.*
Serial No.: 09/313,524
Filed: May 17, 1999
For: EPOTHILONES C, D, E AND F PREPARATION AND COMPOSITIONS

Examiner: Laura Stockton
Art Unit: 1626

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REVISED REQUEST FOR INTERFERENCE UNDER 37 CFR §1.607

I. *INTRODUCTION*

Applicants wish to thank Examiner Stockton for the courtesy of telephonic conferences on February 25 and March 11, 2004, at which time the present request was discussed. In light of the complexity of the situation and at the suggestion of the Examiner, this Request is being immediately filed.[1]

A. *The Previous Requests and Subsequent Events*:

Applicants previously requested that three interferences be declared. Each of these would include (*i*) Applicants' present application and (*ii*) one of the following issued patents:

(*i*) US Patent No. 6,156,905 (Schinzer): request of December 4, 2001,

[1] Comments on the two IDS's submitted by the previous attorney will be separately submitted in the near future, also in accordance with the Examiner's request.

(*ii*) US Patent No. 6,242,469 (hereinafter "Danishefsky I"): request of May 15, 2002, and

(*iii*) US Patent No. 6,284,781(hereinafter "Danishefsky II"): request of May 15, 2002.

Since the filing of those requests, however, several significant events have occurred as a result of actions by the respective patentees. The net effect of these events establishes that only a single patentable invention under 37 CFR § 1.601(n) is present and that only a single interference (rather than three) with a single count is required.

Specifically:

(*i*) A disclaimer of all claims was filed by the patentee in US Patent No. 6,156,905, thereby rendering moot Applicants' original request for an interference with that patent.[2]

(*ii*) On June 5, 2003, the owner of Danishefsky I ('469) filed a reissue application, No. 10/454,738 (hereinafter "Danishefsky I Reissue"), adding broadened claim 23.[3] While the need for the requested interference with Danishefsky I remains, that request must now be modified to include the broader albeit overlapping scope asserted in the reissue application. This is analyzed below.

(*iii*) On August 20, 2002, a terminal disclaimer was filed in Danishefsky II, US Patent No. 6,284,781, disclaiming the term extending beyond the expiration of Danishefsky I. (*See*, Official Gazette of July 22, 2003).[4]

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[2] Applicants communicated the filing of this disclaimer to the Examiner on September 10, 2003.

[3] This was assigned to Examining Group 1626 and published in the Official Gazette on August 26,2003.

[4] On the same day, the owner of record of US Patent No. 6,242,469 also disclaimed its term extending beyond that of the *later* issuing US Patent No. 6,284,781. (*See*, Official Gazette of September 23, 2003). Since the term of the *earlier* issued '469 patent could extend past the term of the *later* issued '781patent only through an extraordinary patent extension, this "disclaimer"

These last actions are particularly relevant to the determination of the number of interferences or counts; *i.e.*, determining if the various claims define the *same patentable invention* under the Patent and Trademark Office's rules or *separate patentable inventions* under those rules.

B. *The Need To Involve Both Danishefsky Patents and the Reissue Application*:

First, and in connection with two patents (Danishefsky I and Danishefsky II) being involved with the present application in a single interference, the exceptions delineated in *JD v. SH*, 58 USPQ2d 1468, 1999 WL 33204516 (Bd. Pat. Intf. 1999) and *Louis v. Okada*, 57 USPQ2d 1430, 2000 WL 1922280 (Bd. Pat. Intf. 2000) are highly relevant here.[5] Thus both precedential opinions noted the jurisdictional issues that hypothetically might result when two patents are involved in an interference with an application. These problems can arise for example when a party seeks to add an opponent's patent where that opponent is involved only on the basis of a another patent, not a pending application. The Board noted in *Louis v. Okada*, however, that the problem does not arise when one of the patents proposed to be involved is the subject of a reissue application:

> Also, nothing expressed herein is contrary to any preexisting practice ... of treating a motion to substitute a reissue application for the patent sought to be reissued as a motion to add the reissue application to the interference already involving that patent. It is the addition of an issued patent, not a pending reissue application, to an on-going interference, which causes a problem under 35 U.S.C. § 135(a). 57 USPQ2d at 1433.

Thus no problem arises if the Danishefsky I Reissue *application* and Danishefsky II were involved in an interference.

Likewise, the Board in *JD v. SH* specifically noted that the need for involving two patents of an opponent in a single interefernce could arise where

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signifies an abundance of caution on the part of the patentee in obviating the potential obviousness double patenting situation.

[5] Both opinions involved decisions on preliminary motions but the same principles would appear to apply to the initial declaration of an interference.

both patents claimed the same patentable invention and both blocked the issuance of an opponent's application:

> The case might be different if there were a second SH patent which stands in the way of issuing a patent based on the JD application. If it were necessary for JD to establish priority vis-a-vis two SH patents claiming the same patentable invention, addition of a second SH patent to the interference may well be justified. 58 USPQ2d at 1470.

That clearly is the case here. Thus if both Danishefsky I (and thus Danishefsky I Reissue) and Danishefsky II claim the same patentable invention as Applicants, both would be a bar to the issuance of the latter application.

C. *The Same Patentable Invention Is Claimed*:

We thus turn to the issue of whether the two Danishefsky patents and the present application claim the same patentable invention. 37 CFR §1.601(n) specifies, *inter alia*, that invention "A" is the same patentable invention as an invention "B" when invention "A" is the same as (35 U.S.C. § 102) or is obvious (35 U.S.C. § 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A". There is, as will be seen below, direct overlap between certain claims of Danishefsky II and claims of Danishefsky I. Consequently some claims of the later-issuing (and now terminally disclaimed) Danishefsky II (corresponding to invention "A") would be anticipated under 35 U.S.C. § 102 by claims of Danishefsky I (corresponding to invention "B"), assuming as one must under the test of §1.601(n) that Danishefsky I were prior art. The converse is also true; *i.e.*, Danishefsky I would be anticipated under 35 U.S.C. § 102 by Danishefsky II assuming the claims of the latter were prior art.

As to residual subject matter for which there might not be direct overlap, 37 CFR §1.601(n) also extends to that which is obvious under 35 U.S.C. § 103; *i.e.*, "not identically [claimed]."[6] In filing his terminal disclaimer in Danishefsky II ('781) vis-à-vis Danishefsky I, counsel for the patentee made reference to non-

[6] While 35 U.S.C. § 103 refers to subject matter "not identically *disclosed* or *described*", the premise of 37 CFR §1.601(n) applies the statutory standard to *claimed* subject matter.

statutory obviousness double patenting rejections in related Danishefsky's applications:

> During the prosecution of the patent application that issued as U.S. Patent 6,284,781, no statutory or non-statutory obviousness type double patenting rejection was levied by the Examiner. However, in related patent applications, USSN 09/874,514 and USSN 10/058,695, a statutory double patenting rejection was issued by the Examiner. Terminal disclaimers were filed in each of the applications disclaiming one over the other so as to obviate any non-statutory obviousness type double patenting rejection.
>
> For consistency, patentee has voluntarily chosen to submit a terminal disclaimer on this patent. By submitting this terminal disclaimer, patentee is not admitting that the subject matter claimed in the above-referenced patent is obvious in light of the subject matter claimed in U.S. Patent 6,242,469.

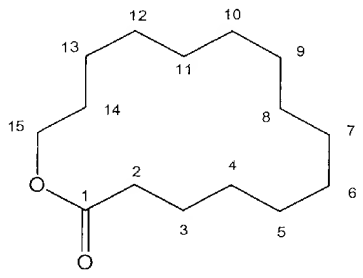
The patentee thus affirmatively took action, solely in the name of consistency, that had no other apparent purpose than obviating a potential obviousness type double patenting rejection. Whether this constitutes an admission of obviousness between the claims of the two patents need not be addressed. As the following analysis demonstrates, not only was counsel's concern with obviousness well founded, claims of the two patents in fact literally overlap. Thus even if counsel's unilateral assertion of non-obviousness were accepted, that assertion is irrelevant: claims in one patent would anticipate (assuming those claims were prior art) claims in the other. In the context of an interference, therefore, the claims of Danishefsky II define the *same patentable invention* under 37 CFR §1.601(n) as those of Danishefsky I. Consequently, separate interferences (and/or counts) would not be proper.

Finally, and as analyzed *infra*, both Danishefsky patents and the Danishefsky Reissue application claim the same patentable invention as Applicants.

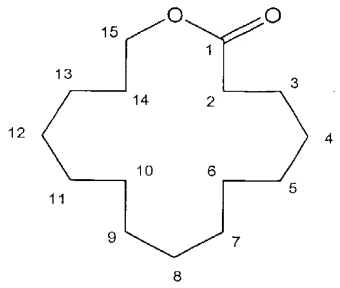
In view of the foregoing events and the following analysis, Applicants herein modify and renew their requests for an interference under 37 CFR §1.607.

II. *NOMENCLATURE CLARIFICATION*

While the parties depict the core structures differently, the compounds claimed by both Danishefsky and Applicants (Reichenbach) correspond to the 16-member cyclic lactone of 15-hydroxypentadecanoic acid:



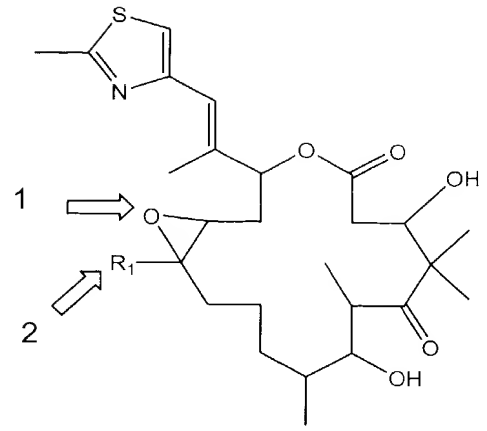
Reichenbach



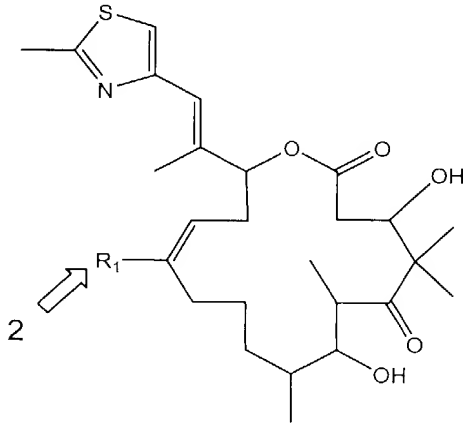
Danishefsky

Moreover, the compounds claimed by both Danishefsky and Applicants carry identical substituents; *i.e.*, two methyl groups in the 4-position and one methyl group in each of the 6- and 8-positions; an oxo group in 5-position, a hydroxy group (or esterified hydroxy group) in each of the 3 and 7- positions, and a 1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl group in the 15-position.

These compounds are species of a class of compounds known as "epothilones". Two epothilones were previously described: epothilone A and epothilone B. Both of these are epoxide compounds (see arrow 1 below) with R_1 being hydrogen in epothilone A (see arrow 2 below) and R_1 being methyl in epothilone B.



The requested interference involves, *inter alia*, epothilone C and epothilone D. In each case the epoxide ring is replaced with a double bond (see *infra*) with R_1 being hydrogen in epothilone C and R_1 being methyl in epothilone D.



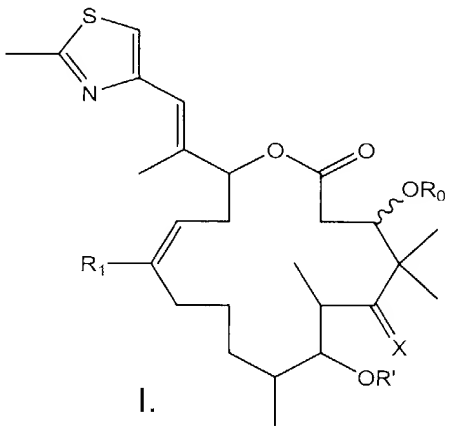
Danishefsky's reference to "desoxyepothilone" apparently refers to the latter unsaturated compounds, the lost oxygen inherent in the "desoxy" nomenclature apparently referring to that in the lost epoxide ring.[7]

[7] Here and elsewhere, Applicants specifically reserve the right to challenge, at the appropriate time, whether Danishefsky's specification and claims comply with 35 U.S.C. § 112.

III. *PROPOSED COUNT*

The annexed Appendix summarizes the information needed for completion of form PTO 850 and provides the proposed count. That proposed count is reproduced below to facilitate the present analysis.

-- An isolated and purified compound of the formula:



I.

wherein

R_1 is hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolan-yl)methyl, hydroxymethyl, or hydroxypropyl,

X is O, and

R_0 and R' are independently hydrogen, acetyl, benzyl, trialkylsilyl, dialkylarylsilyl, or alkyldiarylsilyl; or

a pharmaceutical composition comprising an isolated and purified compound of formula I wherein R_1 is hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolanyl)methyl, hydroxymethyl, or hydroxypropyl, X is O, and R_0 and R' are independently hydrogen or acetyl, in combination with a pharmaceutical carrier; or

a method of treating cancer in a subject suffering therefrom comprising administering to the subject a therapeutically effective amount of an isolated and purified compound of formula I wherein R_1 is hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolan-yl)methyl, hydroxymethyl, or hydroxypropyl, X is O, and R_0 and R' are independently hydrogen or acetyl. --

IV. *SCOPE OF THE PROPOSED COUNT*

Generally an interference count should initially correspond in scope to the broadest claim asserted by the patentee. In that way, the patentee will not be deprived of its best proof for some species falling within that broadest claim but outside the hypothetical narrower count.

A. *Scope of Compounds Defined by the Count*:

The broadest compound scope asserted by the Danishefsky I patent is claim 1. Danishefsky, however, has asserted a broader compound claim in his *reissue application*, namely newly added claim 23. Consequently the scope of the compounds defined by the proposed count corresponds exactly to claim 23 of Danishefsky I Reissue.

B. *Scope of Compositions and Method of Use Defined by the Count*:

In contrast to the claims directed to compounds *per se*, the scope of the compounds utilized in the pharmaceutical compositions and method of use claimed in Danishefsky I is narrower than Reissue claim 23 insofar as R_0 and R' are concerned. Phrased another way, there is no disclosure of pharmaceutical compositions and method of use for compounds in Danishefsky I having the scope of Reissue claim 23. Consequently the count employs a scope of the compounds in the pharmaceutical compositions and the method of use corresponding to claim 1 of Danishefsky I rather than Reissue claim 23; *i.e.*, R_0 and R' are hydrogen or acetyl in defining the pharmaceutical compositions and the method of use of the count.

V. *APPLICATION OF SPECIFIC CLAIMS TO THE COUNT*

Claims 1-22 of Danishefsky I Reissue are identical to claims 1-22 of Danishefsky I. Since the claims of the original patent and reissue application are, with the exception of claim 23, identical, the following analyses of claims 1-22 apply to both Danishefsky I and Danishefsky I Reissue.

A. *DANISHEFSKY I CLAIM 1 (AND DANISHEFSKY I REISSUE CLAIM 1):*

Danishefsky I claim 1 and Danishefsky I Reissue claim 1 correspond to the proposed count since the substituents recited in those claims are literally encompassed thereby; *i.e.*, R_1 is hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolanyl)methyl, hydroxymethyl, or hydroxypropyl, X is O, and R_0 and R' are independently hydrogen or acetyl. This can be seen from the following:

	Count	***Danishefsky I and Danishefsky I Reissue Claim 1***
R_1	hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolanyl)methyl, hydroxymethyl, or hydroxypropyl	hydrogen, methyl, ethyl, propyl, hexyl, 2-(1,3-dioxolanyl)methyl, hydroxymethyl, or hydroxypropyl
X	O	O
R_0 and R'	hydrogen, acetyl, benzyl, trialkylsilyl, dialkylaryl-silyl, or alkyldiarylsilyl	hydrogen or acetyl

B. *DANISHEFSKY I CLAIMS 2-6 AND DANISHEFSKY I REISSUE CLAIMS 2-6:*

Each of Danishefsky I and Danishefsky I Reissue claims 2-6 depends on the respective claim 1 and defines either a subgenus (claims 2-4) or species (claims 5 and 6) of the compounds claimed in claim 1. Claims 2 and 3 restrict R_1 to hydrogen or methyl, respectively, while claim 4 restricts both R_0 and R_1 to hydrogen. Claim 5 restricts all of R_1, R_0, and R' to hydrogen, thus defining a single compound (epothilone C), while claim 6 restricts R_1 to methyl and R_0 and R' to hydrogen, also defining a single compound (epothilone D). Since claims 2-6 define subgenera or species falling within the count, they correspond to the count.

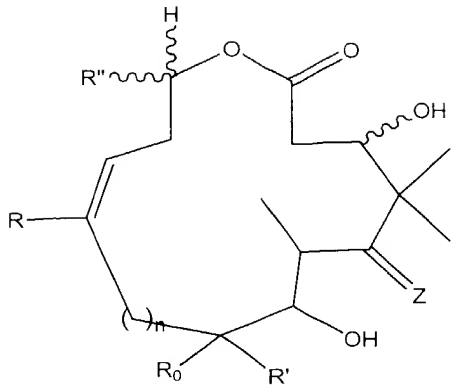
C. *DANISHEFSKY I CLAIM 7 AND DANISHEFSKY I REISSUE CLAIM 7:*

Danishefsky I and Danishefsky I Reissue claim 7 recites a pharmaceutical composition comprising (*i*) a compound falling within either of two depicted classes and (*ii*) a pharmaceutical carrier. The compounds of claim 1 (and thus claims 2-6) are encompassed by the formulae that define the two depicted classes.

Epothilone A and B have been described as being anticancer therapeutics. *See, e.g.*, PCT/EP92/02656, published May 27, 1993. The identical utility is disclosed by Danishefsky I (*see*, col. 2, lines 22-25, col. 28, line 49 to col. 29, line 11); *i.e.*, the compounds are used to treat, prevent, or ameliorate cancer (col. 29, lines 9-11).[8] A therapeutically effective amount of any of the epothilone compounds and a pharmaceutical carrier thus are administered to the subject (col. 28, line 64-col. 29, line 3). The disclosure of suitable route refers to known methods of administration (col. 29, lines 21-27). Compositions may be prepared by any of the methods well known in the art of pharmacy (col. 29, lines 36-38 and lines 58-59). Oral dosage forms for example can employ any of the usual pharmaceutical media, *e.g.*, water (col. 29, lines 39-40). Hence, the carriers are the usual pharmaceutical media and the compositions are compounded by methods well known in the art of pharmacy.

The first of the two formulae set forth in claim 7 at the top of column 71 is as follows:

[8] The compounds are analogized in the "Field of the Invention" to epothilone A and epothilone B which are known anticancer therapeutics (col. 1, lines 21-29).



This formula encompasses the compounds of Danishefsky I claim 1 when:

(*i*) R is hydrogen or alkyl, optionally substituted by hydroxy or cyclic acetal; [col. 71, lines 29, 30 and 31]

(*ii*) R_0 is hydrogen; [col. 71, line 29]

(*iii*) R' (claim 7) is alkyl, specifically methyl (depicted in claim 1);[9] [col. 71, line 30]

(*iv*) R" is -CY=CHX, Y is alkyl, specifically methyl, and X is 2-methyl-1,3-thiazol-4-yl; [col. 71, line 36, 38, and 39]

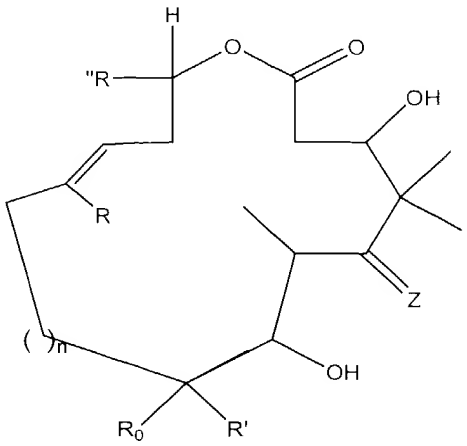
(*v*) Z is oxygen; [col. 71, line 40]

and

(*vi*) n is 3 [col. 71, line 42]

Virtually the identical relationship applies to the second formula in claim 7 (column 71, lines 15-25):

[9] Danishefsky uses the designator R' in two different contexts: in claim 1 in defining the group -OR' in the 7-position, R' is defined as hydrogen or acetyl. In claims 7-22, R' represents a variety of substituents in the 8-position.



The compounds encompassed by this second formula in claim 7 overlap the compounds of claim 1 when:

(*i*) R is hydrogen or alkyl, optionally substituted by hydroxy or cyclic acetal; [col. 71, lines 29, 30 and 31]

(*ii*) R_0 is hydrogen; [col. 71, line 29]

(*iii*) R' (claim 7) is alkyl, specifically methyl; [col. 71, line 30]

(*iv*) R" is -CY=CHX, Y is alkyl, specifically methyl, and X is 2-methyl-1,3-thiazol-4-yl; [col. 71, line 36, 38, and 39]

(*v*) Z is oxygen; [col. 71, line 40] and

(*vi*) n is 2 [col. 71, line 42]

Thus, the compounds defined by claim 7 overlap, and thus are anticipated by, the compounds of claim 1. Since the recited pharmaceutically suitable carriers are admittedly conventional with the compositions being prepared by methods well known in the art of pharmacy, the subject matter of claim 7 would be obvious assuming claim 1 constituted prior art. {*See* 37 CFR §1.601(n)}. Claim 7 thus defines the "same patentable invention" as claim 1.[10]

[10] As is addressed *infra*, claim 7 of Danishefsky I and Danishefsky I Reissue also defines the same patentable invention as claims of Danishefsky II and claims 15, 16, 18, and 19 of Reichenbach.

D. *DANISHEFSKY I CLAIM 8 AND DANISHEFSKY I REISSUE CLAIM 8:*

The preamble of claim 8 as originally printed appears to read upon compounds *per se* without any carrier; a subsequent Certificate of Correction, however, indicates that claim 8 additionally requires a pharmaceutically suitable carrier.

Claim 8 depicts three formulae, the first of which is identical to that in claim 1. The second and third formulae are identical to the two formulae in claim 7. There is no difference in the pharmaceutically suitable carriers recited in claim 8 and those recited in claim 7. The circumstances surrounding the compositions of claim 8, when given its broadest interpretation, thus are the same as those set forth for the compositions of claim 7; *i.e.*, the carriers are the usual pharmaceutical media and the compositions are compounded by methods well known in the art of pharmacy. Since the compounds are the same as those of claim 1 and the compositions otherwise overlap with those of claim 7, claim 8 defines the same patentable invention as claims 1 and 7 in that its subject matter would be anticipated by or obvious over claim 1 or claim 7 assuming either constituted prior art. {37 CFR §1.601(n)}.

The Certificate of Correction states that the "amount of [the] purified compound" in the composition is "effective to inhibit the growth of multidrug resistant cells". Since this language modifies the *amount* of compound in the composition, it does not appear to be a use limitation on the composition.[11] Consequently this language would appear incapable of providing a basis for asserting separate patentability vis-à-vis claim 7 which, as already analyzed, also recites a composition containing a compound and a carrier.

Finally, the Certificate of Correction also states that claim 8 recites the optional presence of an additional cytotoxic agent. The combination of two therapeutic components that together provide unexpected results might corre-

[11] This is to be distinguished from a claim limited to the treatment of resistant cells.

spond to a separate patentable invention; in the context of the language of claim 8, however, the purported presence of an additional component cannot support an assertion of separate patentability for claim 8 for the very reason that the additional component is *optional*.[12] Since its presence is optional, it need not be present. Patentability cannot be based on something that need not be present.

E. *DANISHEFSKY I CLAIM 9 AND DANISHEFSKY I REISSUE CLAIM 9:*

Claim 9 depends upon claim 8 and limits the scope of claim 8 by reciting that the optional cytotoxic agent is "an anticancer agent". While it could be argued that the claim thereby technically differentiates over the claim upon which it depends, the presence of the cytotoxic agent again remains "optional" (since claim 9 depends upon claim 8). Because the broadest construction of claim 9 must encompass compositions in which the additional component is *not* present, separate patentability that is otherwise lacking cannot be generated by the recitation of an *optional* anticancer agent. Thus claim 9, as with claim 8, necessarily defines the same patentable invention as claims 1 and 7 in that its subject matter would be obvious assuming claim 1 or claim 7 constituted prior art. {37 CFR §1.601(n)}.

F. *DANISHEFSKY I CLAIMS 10-13 AND DANISHEFSKY I REISSUE CLAIMS 10-13:*

Claims 10, 11, and 12 each depends upon claim 8 and recites that the optional anticancer agent is adriamycin, vinblastin, or paclitaxel, respectively. Claim 8, however, provides no antecedent basis for the term "anticancer agent". Claim 8 employs the term "cytotoxic agent". Presumably "anticancer agent" means something other than "cytotoxic agent". If not, then claim 9 does not fur-

[12] The foregoing is provided solely to comply with 37 CFR § 1.607 and Applicants concede neither the issue of support under 35 U.S.C. § 112 for the claims of Danishefsky I nor the ultimate patentability thereof.

ther limit, and is identical to, claim 8. Assuming, however, that the antecedent for "the anticancer agent" in claims 10, 11, and 12 is "a cytotoxic agent" in claim 8, the anticancer agent remains "optional" (since each of these claims depends on claim 8). Analogously to claim 8, the claim language encompasses compositions lacking the "optional" component. Accordingly, separate patentability that is otherwise lacking cannot be generated by the presence of an optional ingredient.

Claim 13 depends upon claim 8 and purportedly limits the scope of claim 8 by specifying "the effective amount [of compounds within the scope of claim 8] is between about 0.01 mg/kg to about 40 mg/kg of body weight". The known level of activity for other epothilones falls however within the recited range; *e.g.*, epithilone A was known to have an IC_{50} against the T-24 cell line of <0.05 μM. *See, e.g.*, PCT/EP92/02656, page 13, published May 27, 1993.[13]

The composition of claim 13 encompassing a broad (4,000 fold) range as an amount "effective" would be *prima facie* obvious over, for example, claims 7 or 8 and accordingly does not define a separate patentable invention thereover under the standard of 37 CFR §1.601(n).

G. *DANISHEFSKY I CLAIMS 14-16 AND DANISHEFSKY I REISSUE CLAIMS 14-16:*

Claim 14 defines a method of treating cancer with a compound falling within either of two depicted classes. These two classes are identical with those in claim 7 (discussed above); *i.e.*, the formulae encompass the compounds of Danishefsky I claim 1. Thus the compounds of Danishefsky I claim 1 are

[13] Since the molecular weight of epithilone A is 493, the prior art value of 0.05 μM corresponds to approximately .025 mg/L which for an aqueous solution corresponds to <.025 mg/kg; *i.e.*, the prior art value falls within the range of 0.01 mg/kg to about 40 mg/kg recited in claim 13.

encompassed by the first formula at the top of column 73 in claim 14 (and thus would anticipate those compounds) when:

(*i*) R is hydrogen or alkyl, optionally substituted by hydroxy or cyclic acetal; [col. 73, lines 28-30]

(*ii*) R_0 is hydrogen; [col. 73, line 28]

(*iii*) R' (claim 14) is alkyl (specifically methyl, depicted in claim 1); [col. 73, line 29]

(*iv*) R" is -CY=CHX, Y is alkyl (specifically methyl) and X is 2-methyl-1,3-thiazol-4-yl; [col. 73, line 35-37]

(*v*) Z is oxygen; [col. 73, line 38]

and

(*vi*) n is 3 [col. 73, line 40].

Since the disclosed utility for the compounds of claim 1 is a therapeutic use, namely cancer treatment, and the compounds of claim 1 would anticipate the compounds utilized in the method of claim 14, claim 14 defines the same patentable invention in that its subject matter would be obvious assuming claim 1 constituted prior art {*see* 37 CFR §1.601(n)}.

Claims 15 and 16 depend on claim 14 and define the type of cancer that is treated. Neither claim 15 nor 16, however, restricts the scope of claim 14 insofar as the compounds or method of administration are concerned.

H. *DANISHEFSKY I CLAIMS 17-22 AND DANISHEFSKY I REISSUE CLAIMS 17-22:*

The situation here is analogous to claims 8-13, already discussed *supra*. Claim 17 thus is drawn to a method of inhibiting the growth of multidrug resistant cells. As set forth in the patent, the methods recite contacting the cells with a combination of (*i*) an amount of a compound having one of three structures (the same structures recited in claim 8) and (*ii*) a pharmaceutically acceptable carrier. The amount of the compound in the pharmaceutically acceptable carrier is that said to effective to inhibit the growth of multidrug resistant cells.

According to the subsequent Certificate of Correction, however, the method further comprises *optionally* contacting the multidrug resistant cells with an unspecified amount of a cytotoxic agent.

First, the utility of the compositions of prior claim 8 (discussed *supra*) involves treating multidrug resistant cells. A claim to a "method" in which those compositions are contacted with such cells therefore necessarily would be obvious if not anticipated. Conversely, practicing the method of claim 17 with the recited composition necessarily would anticipate that composition. In the context of an interference, therefore, claim 17 defines the same patentable invention as claim 8 in that its subject matter would be anticipated by or obvious over claim 8 assuming claim 8 constituted prior art {*see* 37 CFR §1.601(n)}.[14] The result recited by the preamble of claim 17, namely, "inhibiting the growth of multidrug resistant cells" is an inherent and necessary result of administering the compounds, *per se*.[15]

In addition, and as with claim 8, claim 17 *optionally* further comprises "contacting the multidrug resistant cells with an amount of a cytotoxic agent". As already discussed, an optional feature cannot confer patentability. Therefore, the method of claim 17 was obvious at the time of the patentees' application in view of the subject matter of claim 14 (as well as claims 1-7) and is thus the same patentable invention under 37 CFR §1.601(n).

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[14] As analyzed *supra*, claim 8 recites a composition comprising an amount of a purified compound ... effective to inhibit the growth of multidrug resistant cells ....

[15] Preambles or phrases of method claims that are not directed to a new use of a known composition, even within the body of the claim, that merely express a purpose or intended result, are not limiting, and therefore may not distinguish the prior art. *Bristol-Myers Squibb v. Ben Venue Laboratories*, 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir., 2001); *see also In re Catalina*, 289 F.3d at 808, 62 USPQ2d at 1785 (Fed. Cir. 2002).

Claim 18 depends upon claim 17 and specifies that the optional cytotoxic agent is "an anticancer agent". Again, analogous to the evaluation of claim 9, *supra*, the necessary construction of the claim does not require the presence of this optional step. Separate patentability that is otherwise lacking cannot be generated by the recitation of an optional step. Therefore, the method of claim 18 does not define a separate invention under 37 CFR §1.601(n) from, for example, claim 14; *i.e.*, assuming a method of treating cancer with a compound of the formulae depicted in claim 14 constituted prior art, the subject matter of claim 18 would have been anticipated or obvious.

.Claim 19, 20, and 21 each depend from claim 18 and specify that the anti-cancer agent is adriamycin, vinblastin, or paclitaxel, respectively. Since "contacting the multidrug resistant cells" with an anticancer agent is *optional* in claim 17, upon which each of these claims ultimately depend, none of claims 19, 20, and 21 requires the presence of this additional agent. Separate patentability that is otherwise lacking thus cannot be generated by a component whose presence is optional. Accordingly, 19, 20, and 21 claims do not define inventions separate from that of claim 14 under 37 CFR §1.601(n).

Claim 22 depends upon claim 17 and, analogous to claim 13, specifies that the effective amount of the compounds is between "about 0.01 mg/kg to about 40 mg/kg of body weight". However, as highlighted in the analysis of claim 13, *supra*, it is not inventive to develop the optimum or workable ranges by routine experimentation. Therefore, the method of claim 22 encompassing a broad (4,000 fold) range as an amount "effective" was *prima facie* obvious at the time of the patentees' application. Accordingly, claim 22 does not define an invention separate from that of claim 8 or claim 17 under 37 CFR §1.601(n).

I. *CLAIM 23 OF DANISHEFSKY I REISSUE CORRESPONDS TO THE COUNT*

Claim 23 of Danishefsky I Reissue follows claim 1 of Danishefsky I, *supra*, with respect to the definitions of R_1 and X but *adds* benzyl, trialkylsilyl, dialkylarylsilyl, and alkyldiarylsilyl to the permissible values for R_0 and R' (in addition to the previously asserted values of hydrogen and acetyl). While claim 23 thus is slightly broader than claim 1 of Danishefsky I, claim 23 would still be anticipated by claim 1 and by the count assuming claim 1 or the count were prior art; *i.e.*, claim 23 defines the same patentable invention as the count and claim 1 of Danishefsky I.[16]

Since the scope of the compounds recited in the proposed count corresponds exactly to the scope of Danishefsky I Reissue application claim 23, claim 23 would be anticipated by the count assuming the count is prior art; *i.e.*, Reissue application claim 23 necessarily defines the same patentable invention as the count under 37 CFR §1.601(n).

VI. *THE CLAIMS OF DANISHEFSKY II CORRESPONDING TO THE COUNT*

The claims of Danishefsky II that correspond to the count are 1, 2, 5-23, 27-30, and 34-37.[17] As has been discussed above, a terminal disclaimer has been filed in Danishefsky II over Danishefsky I. Indeed, and as is now analyzed, the claims of Danishefsky II follow closely the claims of Danishefsky I.

A. *DANISHEFSKY II CLAIMS 1 AND 2:*

Danishefsky II claim 1 recites "[a] pharmaceutical composition comprising a desoxyepothilone macrolide". Claim 2 of Danishefsky II depends upon claim 1

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[16] The foregoing is without prejudice to Applicants' right to challenge compliance of claim 23 with 35 U.S.C. § 112 for, as for example by preliminary motion.

[17] Since the ultimate patentability of the claims of Danishefsky I or II is not before the Examiner, the present analysis is not a concession that claims not designated as corresponding to the count, namely 3, 4, 24, 25, 26, 31, 32, and 33, are patentable.

and specifies the composition further comprising "a pharmaceutically acceptable carrier or diluent".

While the scope and chemical nature of a "desoxyepothilone macrolide" is not apparent from Danishefsky's specification, presumably it relates at least to a lactone of 15-hydroxypentadecanoic acid having a double bond (rather than an epoxy group) between carbon atoms 12 and 13.[18]

First, claim 1 of Danishefsky II does not restrict the claim in any way and, notwithstanding the phrase "pharmaceutical composition", is broad enough to read on a pure compound; *e.g.*, a medicinal powder. Assuming they are prior art, claims 2-6 of Danishefsky I define either a subgenus (claims 2-4) or species (claims 5 and 6) of a "desoxyepothilone macrolide" and thus would anticipate claim 1 of Danishefsky II.

Second, and as noted above, claim 7 of Danishefsky I calls for a pharmaceutical composition comprising epothilone compounds that presumably are "desoxyepothilone macrolides", in combination with a pharmaceutical carrier. Danishefsky II claims 1 and 2 thus would be obvious, if not anticipated, assuming Danishefsky I claim 7 was prior art.

Accordingly, Danishefsky II claims 1 and 2 do not define a separate patentable invention under 37 CFR §1.601(n).

The proposed count recites a pharmaceutical composition comprising what is presumably a "desoxyepothilone macrolide" in combination with a pharmaceutical carrier.

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[18] Applicants also specifically reserve the right to challenge, at the appropriate time, whether the specification and claims of Danishefsky II comply with 35 U.S.C. § 112.

B. *DANISHEFSKY II CLAIMS 6- 22:*

Claim 6 of Danishefsky II recites a method of treating cancer comprising "administering a therapeutically effective amount of a desoxyepothilone to a subject in need thereof." Since the claim recites nothing more than a method of treating cancer by administering an desoxyepothilone and this is already claimed in claim 14 of Danishefsky I, the subject matter of claim 6 of Danishefsky II would be anticipated by or obvious over claim 14 of Danishefsky I, assuming the latter was prior art.

Moreover, and as analyzed above, claim 7 of Danishefsky I describes compositions comprising a compound that presumably is a desoxyepothilone macrolide. The disclosed utility for such compositions is cancer treatment. The pharmaceutical composition of Danishefsky I claim 7 thus would anticipate or render obvious the method of Danishefsky II claim 6, assuming the former was prior art. Claim 6 thus defines the same patentable invention in that its subject matter would be obvious assuming Danishefsky I claim 7 constituted prior art.

The proposed count recites a method of treating cancer by administering to the subject a therapeutically effective amount of what is presumably a "desoxyepothilone macrolide".

C. *DANISHEFSKY II CLAIMS 7-17:*

Each of claims 7-17 depend upon claim 6 and modify the "therapeutically effective amount of the desoxyepothilone". Claim 7, for example, limits the "amount" to a 4,000 fold range, *i.e.*, "between about 0.01 mg/kg to about 40 mg/kg of body weight". Claim 17 refers to the "amount" being effective to kill or inhibit the growth of tumor cells."

As already demonstrated for claim 13 of Danishefsky I, *supra*, limitations such as these do not define a separate patentable invention under 37 CFR

§1.601(n). Moreover this level of activity had been reported for known epothilones (*see*, *e.g.*, PCT/EP92/02656, *supra*).

D. *DANISHEFSKY II CLAIMS 18-20:*

Claims 18-20 of Danishefsky II each ultimately depend upon claim 6 and limit the term "cancer" to various types or subgenera of cancer. However, assuming claim 6 was known, *i.e.*, assuming claim 6 constituted prior art, it would be prima facie obvious to apply the method of treatment as defined by claim 6 to the subgenera of cancer recited in claims 18-20 with a reasonable expectation of success to one of skill in the art at the time of the application. These limitations accordingly do not define a separate patentable invention under 37 CFR §1.601(n).

E. *DANISHEFSKY II CLAIM 21:*

Claim 21 also depends upon claim 6 and modifies the "therapeutically effective amount" by specifying the effective amount is effective to kill or inhibit multidrug resistant cancer. Whatever the scope of this functional language, it must fall within the range recited for claim 6, the claim upon which claim 21 depends, since a dependent claim must incorporate all limitations of the claim upon which it depends. 35 U.S.C. § 112, 3rd paragraph. In the absence of data demonstrating the "kill or inhibit multidrug resistant cancer" range produces unexpected results, claim 21 would be anticipated by or rendered obvious over claim 6 of Danishefsky II. Claim 21 would also be anticipated by or obvious over claims 7 and 14 of Danishefsky I for the same reasons given above. Accordingly, claim 21 would not define a separate patentable invention under 37 CFR §1.601(n).

F. *DANISHEFSKY II CLAIMS 22 AND 23*:

Claim 22 purports to claim a method of treating cancer by administering a composition comprising a desoxyepothilone. Since, as analyzed above for claim 6 of Danishefsky II, this method would be anticipated by or obvious over claim 14 of Danishefsky I, assuming the latter was prior art. Danishefsky I claim 6 thus would anticipate or render obvious the method of Danishefsky II claim 22, assuming the former was prior art. Claim 22 thus defines the same patentable invention in that its subject matter would be obvious assuming Danishefsky I or Danishefsky II constituted prior art.

Claim 23 of Danishefsky II limits the scope of claim 22 to compositions "further compris[ing] a pharmaceutically acceptable carrier or diluent". Incorporating a carrier or diluent that is admittedly conventional, however, would be *prima facie* obvious in view of the subject matter of, for example, claims 1 and 7 of Danishefsky I, or claims 1, 2, or 6 of Danishefsky II, already analyzed. Accordingly claims 22 and 23 do not define separate patentable inventions under 37 CFR §1.601(n).

The proposed count recites a method of treating cancer by administering to the subject a therapeutically effective amount of what is presumably a "desoxyepothilone macrolide".

G. *DANISHEFSKY II CLAIMS 27-28:*

Claims 27-28 are each drawn toward a method of treatment of cancer characterized as resistant to a specified anticancer drug, by administering a *different* known anticancer drug. Claim 27 recites "[a] method for treating paclitaxel-resistant cancer comprising: administering a therapeutically effective amount of a desoxyepothilone to a subject in need thereof, whereby said therapeutically effective amount of said desoxyepothilone is sufficient to kill or inhibit the

growth of tumor cells resistant to paclitaxel." Claim 28 is analogous but is directed to adriamycin-resistant cancer.

Without addressing compliance with 35 U.S.C. § 112, the nature of the drug-resistance does not change the method of treatment. The method of administration is the same whether or not the condition is resistant to some other agent. Moreover, one of skill in the art faced with the problem of a cancer known to be resistant to a given drug would indeed be motivated to administer a different drug known to have anticancer activity. The only other alternatives to administering a different drug are (*i*) administer the drug to which the cancer is known to be resistant or (*ii*) administer nothing, neither of which appears to be particularly responsible.

Finally, and analogously to the analysis of the method of treatment claims presented *supra*, assuming the scope of claim 6, for example, was known, it would be *prima facie* obvious to apply that method of treatment (namely the method defined by claim 6) to the subgenera of cancer recited in claims 27 and 28, *i.e.*, cells resistant to paclitaxel or adriamycin, with a reasonable expectation of success. The limitations of claims 27-28 accordingly do not define a separate patentable invention under 37 CFR §1.601(n).

H. *DANISHEFSKY II CLAIMS 29-30:*

Claim 29 refers to a method of "inhibiting the growth of tumor cells comprising contacting tumor cells with an amount of a composition comprising a desoxyepothilone, effective to kill or inhibit the growth of tumor cells". This language appears to define subject matter identical to that of claim 6.[19] The same

[19] "[T]reatment of cancer" necessarily refers to "inhibiting the growth of tumor cells".

rationale as to why claim 6 does not define a separate invention under 37 CFR §1.601(n) presented *supra*, applies to claim 29.[20]

Claim 30 depends upon claim 29 and specifies that the composition further comprises a pharmaceutically acceptable carrier or diluent. Analogously to the analysis of claim 23 (and of Danishefsky I claims 1 and 7), *supra*, the subject matter of claim 30 also would have been obvious to one of skill in the art at the time of the application,.

I. *DANISHEFSKY II CLAIMS 34-37:*

Claims 34-36 also depend ultimately upon claim 29 and limit the term "tumor cells" to various types of cancer. However, similar to the analysis of claims 18-20 *supra*, assuming claim 6 or claim 29 was prior art, it would be prima *facie* obvious to apply the method of treatment as defined to the subgenera of cancer recited in claims 34-36 and to do so with a reasonable expectation of success. These limitations accordingly do not define a separate patentable invention under 37 CFR §1.601(n).

Claim 37 depends on claim 29 and specifies "the effective amount of the desoxyepothilone is effective to kill or inhibit the growth of multidrug resistant cells."

As analyzed above, a dependent claim must incorporate all limitations of the claim upon which it depends. 35 U.S.C. § 112, 3rd paragraph. One the one hand, therefore, this "effective amount " cannot define a range broader than that defined by claim 29. Assuming the language of claim 37 defines a narrower

[20] *See, e.g.*, the Danishefsky I claim 7 analysis presented *supra*. Danishefsky I claim 7 recites a pharmaceutical composition comprising (*i*) a compound falling within either of two depicted classes, including desoxyepothilones and (*ii*) a pharmaceutical carrier.

range falling within that of claim 29, it is not apparent why that narrower range is patentably distinct from that of claim 29.

Moreover under the premise that the subject matter of claim 1 or claim 7 of Danishefsky I[21] is prior art, one would be motivated to use an "effective amount" of a desoxyepothilone to inhibit the growth of multidrug resistant cells since multidrug resistance of cancer cells was well-recognized as a major obstacle in the use of cytotoxic drugs to control cancer.[22] Accordingly, these functional recitations do not define a separate patentable invention under 37 CFR §1.601(n).

VII. *REICHENBACH CLAIMS CORRESPONDING TO THE COUNT*

The claims of Reichenbach that correspond to the count are 1-4, 15, 16, and 18-20.

A. *REICHENBACH CLAIMS 1-4 AND 20:*

Reichenbach original claims 1 and 2 define epothilone C, the same compound as defined by Danishefsky I claim 5 and Danishefsky I Reissue claim 5. Epothilone C corresponds to the species of the count in which R_1 is hydrogen, X is O, and R_0 and R' are independently hydrogen. It is specifically disclosed on page 2 of the Reichenbach specification and in Example 1.

Reichenbach original claims 3 and 4 define epothilone D, the same compound as defined by Danishefsky I claim 6 and Danishefsky I Reissue claim 6. Epothilone D corresponds to the species of the count in which R_1 is methyl, X is O, and R_0 and R' are independently hydrogen. It is specifically disclosed on page 2 of the specification and in Example 1.

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[21] The disclosed utility for the compounds of Danishefsky I claims 1 and 7 is a therapeutic use, namely cancer treatment, as discussed *supra*.

[22] Ford J. M., *et al.*, *Pharmacologic Circumvention of Multidrug Resistance*, Cytotechnology, 1993;12(1-3):171-212.

Reichenbach claim 20 is generic to epothilone C and epothilone D and corresponds to Danishefsky I claim 4 and Danishefsky I Reissue claim 4 in which R_0 and R' are both hydrogen, R_1 is hydrogen or methyl, and X is O.

B. *REICHENBACH CLAIMS 15, 16, 18, AND 19:*

Reichenbach claims 15, 16, and 18 define compositions containing epothilone C or epothilone D and a carrier. These claims thus define subgenera or species falling under, *inter alia*, claims 7-13 of Danishefsky I and claims 7-13 of Danishefsky I Reissue, and constitute a subgenus or species of the count's language "a pharmaceutical composition comprising a compound of formula I and a pharmaceutical carrier."

Reichenbach claim 19 defines a method of controlling malignant tumors through the administration of epothilone C or epothilone D. It constitutes a subgenera or species of claims 14-22 of Danishefsky I and Danishefsky I Reissue and of the count's language "a method of treating cancer in a subject suffering therefrom comprising administering to the subject a therapeutically effective amount of said compound." Compositions and biological data are disclosed on page 7 and in Experiment 5 on page 17 of Reichenbach's present application.

VIII. *BENEFIT OF GERMAN APPLICATION NO. 196 47 580.5*

Support for Reichenbach claims 1 and 2 (epothilone C) is found in Formula 1 on page 1, and in Example 15 on pages 20-23, of German application No. 196 47 580.5, filed November 18, 1996.[23] Support for Reichenbach original claims 3 and 4 (epothilone D) is found in Formula 1 on page 1, and in Example 15 on pages 20-23, of German application No. 196 47 580.5. Claim 13 on page 29 of German application No. 196 47 580.5 discloses therapeutic compositions and their use as cytostatic agents. Support in German application No. 196 47 580.5 for claim 20 is identical to that discussed above.

[23] All page references are to the English language translation previously filed.

IX. *COMPLIANCE WITH 35 U.S.C. § 135(c)*

Claims 1-4, 15, and 16 of Reichenbach's present application were asserted when that application was filed on May 17, 1999, *i.e.*, approximately two years before the issuance of Danishefsky I on June 5, 2001. Clearly there is compliance with 35 U.S.C. § 135(c) where the subject matter is claimed prior to issuance of the patent.[24]

Moreover, interferences with Danishefsky I and Danishefsky II were formally requested on May 15, 2002, eleven months after the issuance of Danishefsky I, at which time claims 18-20 were added. Consequently Reichenbach is in full compliance with 35 U.S.C. § 135(c) with all claims that correspond to the count being asserted within one year of issuance of Danishefsky I.

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[24] *See, e.g., Stalego v. Heymes*, 263 F.2d 334, 120 USPQ 473 (CCPA 1959); *Corbett v. Chisholm*, 568 F.2d 759, 196 USPQ 337 (CCPA 1977); *Olin v. Duerr*, 175 USPQ 707 (Bd. Pat. Intf. 1972); *Tezuka v. Wilson*, 224 USPQ 1030, 1036 (Bd. Pat. Int'f. 1984); *Bowen v. Bihlmaier*, 231 USPQ 662 (Bd. Pat. App. & Int. 1986)

X. *CONCLUSION*

For the foregoing reasons, the declaration of an interference in which (*i*) claims 1-22 of US Patent Nos. 6,242,469 , (*ii*) claims 1-23 of reissue application No. 10/454,738, (*iii*) claims 1, 2, 5-23, 27-30, and 34-37 of US Patent No. 6,284,781, and (*iv*) claims 1-4, 15, 16, and 18-20 of the present application correspond to the count. Present applicants should be designated senior party and accorded the benefit of German application No. 196 47 580.5 filed November 18, 1996.

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